REMARKS

Claims 8 and 17-26 are pending. Claims 8, 17 and 25-26 are newly amended. Claims 24 is newly cancelled by Applicant without prejudice. Support for the amendments is found throughout the specification and claims as originally filed, and is discussed further below. No new matter has been entered. Applicant submits that no new issues have been entered by these amendments.

Specifically, support for the newly added claim limitations of claim 8 is found throughout the specification, including;

> ".. the present invention provides a method for monitoring the treatment efficacy of a helminthic parasite preparation for an autoimmune or allergy disease in an animal comprising: (a) administering a composition comprising a helminthic parasite preparation or a fraction thereof to the animal; and (b) determining the level of a regulatory T cell activity in the animal after the administering, where an increase in the level of the regulatory T cell activity after the administering is indicative of the treatment efficacy of the helminthic parasite preparation", paragraph 0016 of the instant specification published as US 20050118655A1.
>
> and
>
> "Dosage of a parasite preparation may be monitored by measuring Th1, Th2 or regulatory cell responses", paragraph 163 of the instant specification published as US 20050118655A1.

Specification

The specification is objected to for containing multiple spelling errors. The term "naive" is misspelled as "nave" throughout the specification.

Accordingly, Applicant has amended the specification to correct the typographical spelling errors.

35 U.S.C. § 102(b)

The rejection of Claims 8, 17-18, 20 and 22-26 is maintained under 35 U.S.C. 102(b) as being anticipated by Weinstock et al. (WO 99/33479).

Anticipation requires that the purported prior art reference disclose each and every limitation of the claim. *Atlas Powder Company et al. v. IRECO incorporated et al.,* 190 F.3d 1342, 1347 (Fed. Cir. 1999).

Applicant respectfully traverses on the grounds that all the limitations of the instantly claimed method as newly amended are not taught by the cited reference of Weinstock et al. (WO 99/33479). The claims include a method step comprising measuring regulatory T cell activity, a method step not taught by Weinstock *et al*.

The Office Action contends on page 3 that the rejected claims merely require that an indicator of regulatory T cell activity be measured, noting that Weinstock discloses measuring the production of various cytokines and cell surface markers, including IL-4, IL-5, TGFβ and IFNγ.

Applicant submits that even if some cytokine markers of Th1 and Th2 responses overlap with cytokine markers of regulatory T cell responses, the overlap does not render Weinstock et al. anticipatory since two separate entities (Th1/Th2 responses vs. regulatory T cell responses) are being measured by these overlapping cytokine markers. A measurement of a level of a single cytokine has different meanings with respect to the measurement of a Th1 response, a Th2 response or a regulatory T cell response.

However, Applicant has amended the claims to more clearly point out that Applicant's instant method is directed to measuring and assessing regulatory T cell activity (as opposed to Th1 and/or Th2 activity as described in Weinstock). The claims as newly amended require the monitoring the efficacy of administering a helminthic parasite preparation by looking for an increase in the level of the regulatory T cell activity. Weinstock et al. does not disclose a method comprising this limitation.

In noting that Weinstock et al. disclose methods of treating methods of treating diseases associated with an aberrant/enhanced Th1 response by administering a helminthic parasite preparation. Said diseases include Crohn's disease, ulcerative colitis, rheumatoid arthritis, type 1 diabetes mellitus, lupus

erythematosis, Sarcoidosis and multiple sclerosis, the Office Action concludes that consequently, Weinstock et al. anticipate all the limitations of the rejected claim, page 4 of the Office Action.

However, as discussed above, Weinstock does not teach a correlation between increased Tregulatory activity after administration of a helminthic parasite preparation and efficacy of the parasite treatment in treating a TH1 or Th2 related disease. The specification of Weinstock et al. does not teach how to correlate a cytokine level with measuring regulatory T cell responses. In contrast to measuring regulatory T cell responses, as required by the instant claims, Weinstock et al., teaches assessing the presence of a Th1 or a Th2 response, after administering a helminthic parasite preparation.

Specifically, in section D, entitled "Determination of Th1 and Th2 responses", Weinstock et al. discloses:

> " In order to show the efficacy of the present invention, the Th1 and Th2 response must be distinguished. Metawali et al., 1996, J. of Immunol. 157:4546 has shown that in mice, it is possible to distinguish a Th1 from a Th2 response by histologic analysis, and by analysis of cytokine and immunoglobulin profiles. Further, Sandor et al., 1990, J. of Exp. Med-171:2171 has shown that cell surface expression of Fcy3 and MHC Class II molecules afford discrimination. In this procedure, small bowel and colon are examined histologically to determine the degree of mucosal inflammation, eosinophilia and mastocytosis. The latter cell types are indicative of a Th2 response. Mesenteric lymph nodes (MLN) and spleens can be dissociated into single cell suspensions for in vitro culture in microwell plates. Cells (1-2 x 10^7/well) in complete RPMI medium are cultured for up to 72 h in the presence or absence of worm antigen or anti-CD3 and then the supernatants are assayed for cytokines and immunoglobulins. IFN-γ, TNFα and IgG2a characterize a Th1 response, whereas IL-4, IL-5, IgE and IgG1 typify a Th2 reaction. Also, serum can be assayed for cytokine and immunoglobulin concentrations. Furthermore, dispersed inflammatory leukocytes are examined by flow cytometry for Fcγ3 expression on macrophages (Th1) and MHC Class II expression on B cells (Th2). Controls include serum, MLN and spleens from appropriate age-matched, littermate mice that hosted no parasite. Also, there are other markers of the Th1 vs. Th2 responses", emphasis added, pages 21-22 of the Weinstock.

Further, Weinstock et al. does not disclose methods encompassing T regulatory cells, nor the cytokines they secrete, nor their distinguishing cell markers, nor their activity, all of which are encompassed by the instant claims. Thus, Weinstock et al. does not teach how to measure a regulatory T cell response, despite its teaching the measurement of cytokines to measure a Th1 response or a Th2 response.

Accordingly, Weinstock does not teach treating diseases associated with an aberrant/enhanced Th1 response by administering a helminthic parasite preparation, AND monitoring the treatment's efficacy by looking for an increase in Treg activity after parasite administration, as required by the claims as newly amended.

Because Weinstock does not teach a method comprising determining the measuring regulatory T cell responses as required by the instant claims, Applicant respectfully submits that Weinstock is not prior art, and accordingly does not anticipate the instant claims.

35 U.S.C. § 103(a)

Claims 8 and 17-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Weinstock et al (WO 99/33479).

Applicant respectively traverses.

Graham v. John Deere Co., 338 U.S. 1, 148 USPQ 459 (1966), recently reaffirmed by *KSR International Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 82 USPQ2d 1385 (2007), provides the analytical framework for determining obviousness. Under *Graham*, obviousness is a question of law based on underlying factual inquires that address (1) the scope and content of the prior art, (2) the differences between the claimed invention and the prior art, and (3) the level of ordinary skill in the pertinent art. Evidence of secondary factors (e.g., commercial success, long-felt but unmet need, and unexpected results) are also given weight in the analysis.

Moreover, to establish a prima facie obviousness rejection of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974).

Predictability is required in maintaining a legal conclusion of obviousness under both KSR and the USPTO published guidelines.

Independent Claim 8, as newly amended, is drawn to a method for treating an animal with a Th1 or Th2 related disease comprising administering a helminthic parasite preparation that alters a regulatory T cell activity to said animal; and measuring regulatory T cell responses.

As discussed in the above rebuttal to the 102 rejection, Weinstock et al. do not teach all the limitations of the claims as newly amended, in particular the recited limitation of measuring regulatory T cell activity. Weinstock et al. does not teach measuring regulatory T cell responses.

In contrast to the methods of the instant invention which comprise measuring regulatory T cell activity after administering a helminthic parasite preparation in order to show efficacy of treatment, the methods disclosed by Weinstock et al. comprise determining Th1 and Th2 responses by measuring the production of various cytokines and cell surface markers after administering a helminthic parasite preparation in order to show efficacy of treatment.

In noting that the specification discloses that activity of regulatory T cells can be determined by measuring a myriad of cytokine and/or surface cell markers including CD4, IL4, IL-5, TGFβ and IFNγ, the Office Action indicates on page 6 that the instantly claimed method is obvious "[g]iven that Weinstock et al. disclose the determination of Th1 and Th2 responses after treatment with the claimed composition "in order to show efficacy" of their method (see page 21) and said responses were determined by measuring the production of various cytokines and cell surface markers include IL4, IL-5, TGFβ and IFNγ (see pages 21-25)".

While not refuting Weinstock's methods relating to Th1 and Th2 responses, Applicant fails to see how these teachings by Weinstock relating to Th1 and Th2 responses provide any teaching or motivation for measuring T regulatory cell activity as required by the instant claims. That there is overlap in the tools (various cytokines and cell surface markers) used to measure activities of a Th1 response and/or a Th2 response disclosed by Weinstock with the tools (various cytokines and cell surface markers) used to measure activities of a Treg response as instantly claimed, Weinstock does not provide a teaching or suggestion to look at Treg activity after helminth administration. For instance, a ruler can be used to measure ants, but methods comprising the measurement of ants using a ruler provides no motivation to measure grasshoppers near the ant colony.

KSR emphasizes the importance of identifying "a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does" in an obviousness determination, *KSR Intern. Co. v. Teleflex Inc.,* 127 S.Ct. 1727, 1731.

The novelty of Applicant's invention is its use of Tregulatory cell activity to monitor treatment comprising the administration of a helminth parasite preparation. Weinstock does not teach or suggest the use of Treg cells in any method, let alone the instantly claimed method.

The Office Action states on page 7 that "[g]iven that there is significant overlap between the markers of various Th1, Th2 and regulatory T cells, the cited reference renders the instant claims obvious". Applicant does not follow this argument. Even if the exact same markers were used, Applicant notes the distribution and amount of said markers differs between Th1 cells, Th2 cells and Treg cells.

The Office Action states also on page 7 that "given that Weinstock et al. disclose the methods by which cell markers can be measured (e.g. ELISAs and flow cytometry), the skilled artisan would have had a reasonable expectation of success".

Applicant notes that a reasonable expectation of success does not lie in the fact that known cell surface markers and cytokines can be used to measure T regulatory activity.

Instead a prima facie case of obviousness requires that one of skill at the time of the invention would have had a reasonable expectation of success in using measurements of Tregulatory activity to monitor a treatment comprising the administration of a helminth parasite preparation. Weinstock does not teach that T regulatory activity can be used to predict the efficacy of a treatment comprising the administration of a helminth parasite preparation. Before Applicant's teaching, how would one of skill in the art know that there would even be any Treg activity to measure after administering a helminth preparation, since Weinstock does not teach anything about Tregulatory cells in the context of helminth parasite administration treatment. Thus, Applicant submits the predictability regarding measuring T regulatory activity in a method comprising the administration of a helminth parasite preparation which is required in maintaining a legal conclusion of obviousness under both *KSR* and the USPTO published guidelines is missing.

Regarding Claims 19 and 21:

In acknowledging that Weinstock et al. differs from the instant invention by not explicitly disclosing the regulatory T cell markers recited in claims 19 and 21, the Office Action nevertheless indicates on page 7 that it would have been "obvious for the skilled artisan to use them in the methods of Weinstock et al. for determination of Th1 and Th2 responses after treatment with the claimed composition 'in order to show efficacy of their method", citing *KSR* and stating "since the use of screening of the recited T cell activation markers is well known in the art", emphasis added.

However, the Office Action provides no explanation of how the phrase "T cell activation markers" relates to the instantly claimed method comprising measuring regulatory T cell responses/activities, nor how "T cell activation markers" relates to markers used to measure regulatory T cell activity as recited in the instant dependent claims.

KSR emphasizes the importance of identifying "a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does" in an obviousness determination, *KSR Intern. Co. v. Teleflex Inc.,* 127 S.Ct. 1727, 1731.

Applicant respectfully submits that no reason has been provided by the Office Action for measuring the activity of Treg cells, in any manner, nor for measuring Treg activity using the specific markers recited in claims 19 and 21, in the instantly claimed method. Nor does Weinstock teach the second step of the instantly claimed method – that of measuring regulatory T cell responses after administering a helminthic preparation. Further, nowhere in the motivation of the office action, nor in the cited art, is there provided a reason to look at markers of T regulatory cells, in the claimed method of administering a helminthic parasite preparation, including those recited in the instant dependent claims. Thus, the instant claims are not a further characterization of a known method, but provides a means, in one embodiment to monitor the effectiveness of the administered dose.

Recent case law dictates that a finding of obviousness requires that the prior art provide evidence that that the suggestion would be successful. *In re Kubin*, 2008-1184 (Fed. Cir. April 3, 2009)(Serial No. 09/667,859) quotes O'Farrell (853 F.2d. 894, 903 (Fed. Cir. 1988), adding emphasis to the phrase "detailed enabling methodology" by underlining it

> "specifically this court observed that an obviousness finding was appropriate where the prior art contained a detailed enabling methodology for practicing the claimed invention, a suggestion to modify the prior art to practice the claimed invention and evidence suggesting that it would be successful." 853 F.2d at 902 .

In the absence of documentary prior art providing a disclosure that measuring regulatory T cell responses would be applicable in a method for treating an animal with a Th1 or Th2 related disease, as encompassed by the instantly claimed methods, Applicants respectfully submits that one of skill at the time of the invention would not have had a reasonable expectation of success in practicing the methods of the instant claims, e.g., for example in monitoring dosage. .

Therefore, without the benefit of Applicant's specification, one of skill could not have reliably predicted a method that encompassed measuring regulatory T cell responses in the treatment of Th1 or Th2 related diseases after the administration of a

helminthic parasite preparation. Without evidence that one of skill in the art could have predictably arrived at the claimed invention based on the teachings of Weinstock et al., and not based on the teachings of the instant specification, a *prima facie* case of obviousness under *KSR* has not been achieved. Without a teaching of all the limitations of the claims, including the step of measuring Tregulatory activity, a *prima facie* case of obviousness under *In re Royka*, has not been achieved

Conclusion

Applicant submits that all claims are allowable as written and respectfully requests early favorable action by the Examiner. If the Examiner believes that a telephone conversation with Applicant's attorney's/agent would expedite prosecution of this application, the Examiner is cordially invited to call the undersigned attorney/agent of record.

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